

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

205422Orig1s000

205422Orig2s000

Trade Name: REXULTI Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.

Generic Name: brexpiprazole

Sponsor: Otsuka Pharmaceutical Company, Ltd.

Approval Date: July 10, 2015

Indication: Provides for the use of REXULTI (brexpiprazole) 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg Tablets for the following indications which, for administrative purposes, we have designated as follows:

- NDA 205422/Original-1 - Adjunctive Treatment of Major Depressive Disorder
- NDA 205422/Original-2 - Treatment of Schizophrenia

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205422Orig1s000

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RESEARCH**

APPLICATION NUMBER:

205422Orig1s000

205422Orig2s000

APPROVAL LETTER



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 205422/Original-1
NDA 205422/Original-2

NDA APPROVAL

Otsuka Pharmaceutical Company, Ltd.
Attention: Patrick F. Guinn, RAC
Director, Global Regulatory Affairs
Otsuka Pharmaceutical Development & Commercialization, Inc.
2440 Research Boulevard
Rockville, MD 20850

Dear Mr. Guinn:

Please refer to your New Drug Application (NDA) dated and received July 11, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for REXULTI (brexpiprazole) Tablets 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg.

We acknowledge receipt of your amendments dated:

August 1, 2014	October 13, 2014	February 4, 2015	June 2, 2015
August 5, 2014	October 14, 2014 (2)	February 5, 2015	June 3, 2015
August 7, 2014	October 30, 2014	February 10, 2015	June 4, 2015
August 22, 2014	November 10, 2014	February 12, 2015	June 10, 2015
August 29, 2014	November 17, 2014	February 13, 2015(2)	June 15, 2015
September 5, 2014	December 12, 2014	February 18, 2015	July 6, 2015
September 8, 2014	December 24, 2014	February 27, 2015	July 9, 2015
October 7, 2014	January 30, 2015	April 14, 2015	July 10, 2015

This new drug application provides for the use of REXULTI (brexpiprazole) 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, and 4 mg Tablets for the following indications which, for administrative purposes, we have designated as follows:

- NDA 205422/Original-1 - Adjunctive Treatment of Major Depressive Disorder
- NDA 205422/Original-2 - Treatment of Schizophrenia

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling text.

We approve the Comparability Protocol for Removal of Release Testing for [REDACTED] (b) (4) [REDACTED] in the Drug Substance.

WAIVER OF HIGHLIGHTS SECTION

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE CONTAINER LABELS

Submit final printed carton and immediate container labels that are identical to the enclosed carton and immediate container labels submitted on June 15, 2015, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008)*. Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 205422.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product(s) with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

ADVISORY COMMITTEE

Your application for REXULTI (brexpiprazole) was not referred to an FDA advisory committee because the clinical trial designs are similar to previously approved products for the adjunctive treatment of major depressive disorder and schizophrenia. Additionally, evaluation of the effectiveness and safety data did not raise significant safety or efficacy issues in the adult adjunctive major depressive disorder population or schizophrenia population.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

NDA 205422/Original-1 - Adjunctive Treatment of Major Depressive Disorder (MDD)

We are waiving the pediatric study requirement for ages 0 to 6 years because necessary studies are impossible or highly impracticable. This is because of the low prevalence of MDD requiring adjunctive treatment in this age group.

We are also waiving the pediatric study requirement for ages 7 to 17 years because brexpiprazole is not likely to yield a meaningful therapeutic benefit over existing therapies for pediatric patients, and it is not likely to be used in a substantial number of pediatric patients.

NDA 205422/Original-2 - Treatment of Schizophrenia

We are waiving the pediatric study requirement for ages 0-12 years for children with schizophrenia because onset of schizophrenia prior to 13 years of age is rare.

We are deferring submission of your pediatric studies for ages 13 to 17 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required by section 505B(a) of the FDCA are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

- 2929-1 Deferred pediatric study under PREA for the treatment of schizophrenia in pediatric patients aged 13 to 17. Conduct a study to obtain pharmacokinetic, safety, and tolerability data and provide information pertinent to dosing brexpiprazole in the relevant pediatric population.

Final Protocol Submission: 03/2014 (Submitted)
Study/Trial Completion: 05/2016
Final Report Submission: 11/2016

- 2929-2 Deferred pediatric study under PREA for the treatment of schizophrenia in children aged 13 to 17 years. Conduct a Phase 3, Efficacy: multicenter, randomized, double-blind trial with two phases: Phase 1 - placebo- and active-controlled, short-term (6 weeks) study; Phase 2 – active-controlled long-term

extension (26 weeks) study. Goal of both phases is to obtain data on the efficacy and safety of brexpiprazole in the relevant pediatric population.

Final Protocol Submission: 06/2016
Study/Trial Completion: 12/2020
Final Report Submission: 06/2021

- 2929-3 Deferred pediatric study under PREA for the treatment of schizophrenia in adolescents aged 13 to 17 years. Conduct a Phase 3, Safety: open-label, multicenter, long-term (2 years) study to obtain data on the safety of brexpiprazole in the relevant pediatric population.

Final Protocol Submission: 06/2016
Study/Trial Completion: 12/2022
Final Report Submission: 06/2023

Submit the protocols to your INDs 101871, with a cross-reference letter to this NDA.

Reports of this/these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS SUBJECT TO REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of the following postmarketing commitments and the timetable you agreed to on July 8, 2015:

- 2928-1 A placebo-controlled, randomized withdrawal maintenance study of brexpiprazole in patients who require adjunctive treatment of major depressive disorder.

Final Protocol Submission: 03/2016
Trial Completion: 12/2021
Final Report Submission: 06/2022

- 2929-4 A placebo-controlled, randomized withdrawal maintenance study of brexpiprazole in patients with schizophrenia.

Final Protocol Submission: 09/2012 (Submitted)
Trial Completion: 02/2015 (Completed)
Final Report Submission: 10/2015

Submit the clinical protocols to your IND 103958 and 101871 for this product. Submit the postmarketing final report to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled **“Postmarketing Commitment Protocol,” “Postmarketing Commitment Final Report,” or “Postmarketing Commitment Correspondence.”**

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert, Medication Guide, and patient PI (as applicable) to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at <http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

METHODS VALIDATION

The Division of Pharmaceutical Analysis (DPA) completed their evaluation of the methods validation information and found the evaluated analytical procedures acceptable for quality control and regulatory purposes. DPA recommends the following clarifications to the sample calculations for assay:

Assay for 2, 3 and 4 mg tablets (b) (4)

Assay for 0.25, 0.5 and 1 mg tablets (b) (4)

1. (b) (4) DPA recommends the equations be amended as follows:

(b) (4) for 0.25 mg tablet
(b) (4) for 4 mg tablet

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, contact CDR Kofi Ansah, Pharm.D., Senior Regulatory Project Manager, at (301)796-4158 or email: Kofi.Ansah@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Ellis F. Unger, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
Carton and Container Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ELLIS F UNGER
07/10/2015